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10/691,045	10/21/2003	De-Chao Yu	CELL-018CON	8701

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EXAMINER

MARVICH, MARIA

ART UNIT PAPER NUMBER

1636

DATE MAILED: 03/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/691,045

Applicant(s)

YU ET AL.

Examiner

Maria B Marvich, PhD

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE ____ MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☐ Claim(s) ____ is/are pending in the application.
- 4a) Of the above claim(s) ____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) ____ is/are allowed.
- 6) ☐ Claim(s) ____ is/are rejected.
- 7) ☐ Claim(s) ____ is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____. |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date ____. | 6) <input checked="" type="checkbox"/> Other: <u>Notice to Comply</u> . |

DETAILED ACTION

This office action is in response to a response to a restriction requirement filed 2/8/05. Claims 1-58 have been canceled. Claims 59-88 have been added. Claims 59-88 are pending in this application.

Election/Restrictions

Applicant's election with traverse of Group I (Claims 1-54) in the reply filed on 2/8/05 is acknowledged. Applicants have cancelled claims 1-58 and added claims 59-88. Newly added claims 59-87 correspond to the invention of Group I. Newly added claim 88 corresponds to the invention of Group II. Therefore, claim 88 is drawn to non-elected subject matter and is therefore withdrawn from consideration.

Applicants' traversal is on the ground that examination of all currently pending claims would not pose an undue burden on the Examiner.

Applicants' traversal has not been found persuasive for the following reasons. Search Burden exists if the inventions (1) have a separate status in the art, (2) have different classification, (3) have same classification but recognition of divergent subject matter, (4) have divergent fields of search, or (5) have search required for one group not required for the other. In the instant application, the inventions of Group I and Group II have a separate status in the art as demonstrated by their different classification and divergent subject matter. Furthermore, a search for art pertaining to each group is not coextensive and therefore a search for art for a replication competent adenovirus does not overlap a search for methods of producing an adenovirus. Prior art that teaches the vector, would not necessarily be applicable to the method

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of propagation of the vector. Moreover, even if the product were known, the method of propagation of a vector or selective cytotoxicity may be novel and unobvious in view of the preamble or active steps. Therefore, searching the inventions of Groups I and II together would impose serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

Information Disclosure Statements filed 10/21/03 and 9/16/04 have been identified and the documents considered. The signed and initialed PTO Form 1449s has been mailed with this action.

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Specifically, figure 9, table 4 on page 86, page 90, line 20 and line 22, page 91, line 16 and line 17, and table 6 on page 94 contain sequences that are not identified by sequence identifier numbers. If the sequences can be found in the sequence listing it would be remedial to insert the appropriate SEQ ID NO:s. If not, a new sequence listing, CRF and letter stating that the contents of the sequence listing and the CRF are the same and contain no new matter are required.

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Claim Objections

Claims 67, 69, 82 and 83 are objected to because of the following informalities: HSV-tk, GM-CSF, IFN, TNF, NGF, EMCV and VEGF are abbreviated. For clarity, the first occurrence of an abbreviation in the claims should be spelled out for clarity. Appropriate correction is required.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 59-87 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3 and 5-38 of US Patent 6,692,736.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the

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reference claims because both sets of claims recite a replication competent adenoviral vector comprising first and second genes separated by an IRES in which the genes are under transcriptional control of a transcriptional regulatory element (TRE) and the second gene has a deletion in its promoter. The claims of U.S. 6,692,736 recite that the vector exhibits greater specificity for the target cell than an adenovirus vector comprising a target cell-specific TRE operably linked to a gene and lacking an IRES. It would have been obvious to one of ordinary skill at the time of the invention was made that the vector of the instant invention also have great specificity for the target cell than a vector without the TRA and lacking an IRES because the instant invention teaches that it is within the ordinary skill of the art to generate a adenovirus vector comprising a TRE and an IRES and because U.S. 6,692,736 teaches that it is within the ordinary skill of the art to generate a vector with increased target cell specificity. One would have been motivated to do so in order to receive the expected benefit of a vector with target cell specificity. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

The claims of U.S. Patent 6,692,736 differ from the instant claims 62-73 in that U.S. Patent 6,692,736 fails to recite specifically preferred TRE sequences and to be used as well as transgenes included in the vector. However, U.S. Patent 6,692,736 discloses that preferred TREs include PSA, PB, AFP, a cell status, melanocyte cell-specific, mucin, uroplakin, hKLK2, E2F-1, MART-1 and UP. Furthermore, the U.S. Patent 6,692,736 discloses that desirable transgenes include HSV-tk, cytosine deaminase, genes that encode A chains of diphtheria toxin, ricin or abrin, genes encoding a factor capable of initiating apoptosis, the Fas gene, cytokines, antigens,

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transmembrane proteins, and the like, such as IL-1, IL-2, IL-6, IL-12, GM-CSF, G-CSF, M-CSF, IFN- α , TNF- α , TGF- α , NGF or a reporter such as CAT or luciferase. It would have been obvious to one having ordinary skill in the art to modify the vector of claims 62-73 by selecting a specifically disclosed embodiment that supports claim 31 of U.S. patent 6,692,736 i.e. the specifically disclosed embodiments in U.S. patent 6,692,736. One having ordinary skill in the art would have been motivated to do this because the embodiment is disclosed as being a preferred embodiment with in claim 31.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding a patent from U.S. Patent 6,692,736, then two different assignees would hold a patent to the claimed invention of U.S. Patent 6,692,736, and thus improperly there would be possible harassment by multiple assignees.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 61, 67-71, 81 and 82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 61 recites the limitation "said adenoviral gene essential for replication" in claim 59. There is insufficient antecedent basis for this limitation in the claim.

Claim 67 is vague and indefinite in that the metes and bounds of the Markush listing of therapeutic genes are unclear. While the claim recites that the therapeutic genes "are selected from the group consisting of", ricin and abrin are listed in the alternative. Therefore, it is unclear what components form the Markush group.

Claim 80 recites the limitation "said adenovirus" in claim 59. There is insufficient antecedent basis for this limitation in the claim. Claim 59 recites an adenoviral vector whereas, the recitation of adenovirus in claim 80 implies the actual adenovirus particle, which is not encompassed by claim 80.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 59- 62, 65, 67-70, 72, 74-78, 80, 81 and 84-87 are rejected under 35

U.S.C. 102(a) as being anticipated by Chang et al (WO 99/25860; see entire document).

Chang et al teach an adenovirus vector that is selectively replicative and comprises gene for replication under control of a tissue specific promoter that further comprises transgenes. The transgene and the gene essential for replication can be linked by an IRES (see e.g. page 18, paragraph 2, page 29, paragraph 2 and figure 7). The gene essential for replication is any adenoviral gene that is essential for replication such as early or late genes (see e.g. page 15, paragraph 5). Specifically cited are E1A, E1B, E2, E3 or E4 (see e.g. bridging paragraph page

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21-22). However, the specification teaches that the gene is essentially any gene that is required for the life cycle of the virus, which inherently includes late genes (see e.g. page 32, paragraph 2). Tissue specific promoters contemplated for use are mucin, CEA, PSA, tyrosinase or AFP (see e.g. page 29, paragraph 4). Cytotoxic genes include diphtheria toxin A, HSV-tk.

Alternatively the transgene can be a cytokine such as GM-CSF or a reporter gene (see e.g. figure 1B, bridging paragraph 30-31 and page 29, paragraph 5). The first gene has a mutation in the transcriptional regulatory region, which comprises promoters and enhancers (see e.g. bridging paragraph page 17-18 and page 18, paragraph 2). It is inherent in the design of the construct that the second promoter be deleted of its endogenous promoter as the use of the IRES is for expression of the two genes by a single regulatory sequence (see e.g. page 18, paragraph 2).

Cells and composition comprising the adenovirus are taught (see e.g. example 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 63, 64, 66 and 73 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Yu et al (Cancer Research, 1999; see entire document) or Lin et al (PNAS, 1995; see entire document) or Roelvink et al (US 2001/0047081; see entire document).

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Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of a TRE that is from human glandular kallikrein or uroplakin or E2F-1. Chang et al do not teach that the transgene is a reporter such as luciferase or β -galactosidase.

Yu et al teach identification of the transcriptional regulatory sequence of human kallikrein 2 (hK2) that is selectively inducible in prostate to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Yu et al generated a recombinant adenovirus comprising the hK2 promoter driving expression of luciferase to assay its activity and inducibility (see e.g. figure 1). Furthermore, to generate a selective replicating adenovirus, hK2 was used to express E1b in a vector also comprising E1A (see e.g. fig 4).

Lin et al teach identification of a promoter that is selectively expressive in the suprabasal urothelial cells (see e.g. abstract). The urothelial promoter sequences are linked to a reporter gene, β -galactosidase and its tissue specificity was assayed. The promoter was expressive only in bladder (see e.g. figure 4 and 5).

Roelvink et al teach that the E2F promoter provides targeted gene expression in prostate cancer cells (see e.g. paragraph 0023).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the tissue specific promoter taught by Chang et al with the kallikrein

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promoter or uroplakin II promoter or E2F promoter taught by Yu et al or Lin et al or Roelvink et al because Chang et al teach that it is within the ordinary skill of the art to generate a selectively replicating adenovirus by introducing a tissue specific promoter into the adenovirus and because Yu et al and Lin et al and Roelvink et al teach that it is within the ordinary skill of the art to use kallikrein, E2F and uroplakin promoters for tissue specific expression. One would have been motivated to do so in order to generate potential therapeutics in which adenovirus are selectively replicative in neoplasia (see e.g. Yu et al, page 1503, col 2). Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 71 and 79 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Perez and White (Journal of Cell Biology, 1998; see entire document).

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of Fas as the cytotoxic gene in which E1B 19K is deleted.

Perez and White teach that Fas mediated apoptosis leads to cell killing triggered by Fas ligand. E1B 19K blocks Fas mediated apoptosis (see e.g. abstract). It would have been obvious

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to delete E1B 19K in an adenovirus carrying FAS for the cytotoxic effects of Fas mediated apoptosis to occur.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the cytotoxic transgene expressed by the adenovirus taught by Chang et al with a FAS gene in which the E1B 19K gene is deleted or mutated based upon the teachings of Perez and White because Chang et al teach that it is within the ordinary skill of the art to express a cytotoxic gene from adenovirus for cell killing and because Perez and White teach that Fas cell killing is blocked by E1B 19K. One would have been motivated to do so in order to receive the expected benefit of unhampered apoptotic cell killing in conditions taught by Chang et al in which cell killing is desired. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 82 and 83 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chang et al (WO 99/25860; see entire document) in view of Stein et al (Molecular and Cellular Biology, 1998; see entire document) or Borman et al (NAR, 1995; see entire document).

Applicants claim a replication competent adenovirus comprising an adenovirus gene separated from a second gene in which expression of the bicistron is controlled by a tissue specific regulatory element.

The teachings of Chang et al are described above and are applied as before except;

Chang et al do not teach use of specific IRES sequence such as from EMCV or VEGF.

Stein et al teach isolation and utilization of the VEGF IRES that is effective in promoting cap-independent translation of mRNA (see e.g. abstract). Stein et al teach that the advantage of the VEGF IRES is the capacity for cap-independent translation in situations when overall protein synthesis is compromised (see e.g. page 3115, col 2). Internal ribosome entry is said to improve the competition with other mRNAs which otherwise would have rendered the translation of the mRNA an inefficient process (see e.g. page 3118, col 1).

Borman et al compare the activity of a variety of IRES sequences. EMCV is the most efficient at mediating expression (see e.g. figure 3).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the IRES taught by Chang et al with the VEGF IRES sequence such as described by Stein et al or the EMCV IRES as described by Borman et al because Chang et al teach that it is within the ordinary skill of the art to express a bicistronic and because Stein et al and Borman et al teach that it is within the ordinary skill of the art to use IRES for bicistronic expression. One would have been motivated to do so in order to receive the expected benefit of cap-independent translation in situations when overall protein synthesis is compromised or for highly efficient expression. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD can be reached on (571)-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9306 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Maria B Marvich, PhD
Examiner
Art Unit 1636

March 4, 2005


GERRY LEFFERS
PRIMARY EXAMINER

Notice to Comply	Application No.	Applicant(s)	
	10/691045	Yu et al	
	Examiner	Art Unit	
	M. Marvich	1636	

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

Applicant must file the items indicated below within the time period set the Office action to which the Notice is attached to avoid abandonment under 35 U.S.C. § 133 (extensions of time may be obtained under the provisions of 37 CFR 1.136(a)).

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 C.F.R. 1.821 - 1.825 for the following reason(s):

- ☒ 1. This application clearly fails to comply with the requirements of 37 C.F.R. 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rulemaking notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- ☐ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 C.F.R. 1.821(c).
- ☐ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 C.F.R. 1.821(e).
- ☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitted. However, the content of the computer readable form does not comply with the requirements of 37 C.F.R. 1.822 and/or 1.823, as indicated on the attached copy of the marked -up "Raw Sequence Listing."
- ☐ 5. The computer readable form that has been filed with this application has been found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A Substitute computer readable form must be submitted as required by 37 C.F.R. 1.825(d).
- ☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable from of the "Sequence Listing" as required by 37 C.F.R. 1.821(e).
- ☒ 7. Other there are sequences in the specification that are not accompanied by SEQ ID NO;s.

Applicant Must Provide:

- ☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing".
- ☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification.
- ☒ A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d).

For questions regarding compliance to these requirements, please contact:

For Rules Interpretation, call (703) 308-4216

For CRF Submission Help, call (703) 308-4212

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